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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/520,946	08/30/95	BROW M	FORS-01755

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1805	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No. 08/520,946	Applicant(s) Brow, Lyamichev And Olive
	Examiner WILLIAM SANDALS	Group Art Unit 1805

☒ Responsive to communication(s) filed on *Jun 9, 1997*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-29, and 31-54* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-29, and 31-54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. The amendment to claim 1 has overcome the rejection under 35 USC 112, first paragraph and 35 USC 101, and the rejection is withdrawn.

Also the amendment to the specification has cured the defects objected to in the First Action On the Merits, and the Objection is withdrawn.

Response to Arguments

2. Applicant's arguments filed June 9, 1997, have been fully considered but they are not persuasive.

Applicants have argued that the Lyamachev et al. reference does not teach intrastrand cleavage of the hairpin structures of the claims. Lyamichev et al. at page 779, column 1, and in Figure 1, and at page 781, column 3, and again at page 782, columns 1 and 2 taught the cleavage of the hairpin structure by the nuclease.

Applicants have argued that the Lyamichev et al. reference does not teach substrate cleavage without a second (pilot) oligonucleotide primer. Lyamichev et al. at page 779, column 1, and in Figure 1, and at page 781, column 3, and again at page 782, columns 1 and 2 taught the cleavage of the hairpin structure by the nuclease.

Applicants have argued that the Lyamichev et al. reference does not teach PCR for the isolation of a polymorphic locus. Lyamichev et al. at page 782, column 3 contemplates just such an experiment.

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, applicant's argument that the teachings of Young et al. and Seela and Roling did not teach the claimed invention, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981)..

The rejection under 35 USC 103 (a) is repeated infra.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-29 and 31-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyamichev et. al. in view of Young, Seela and Roling, and Young et. al..

The claims are drawn to a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus (HCV) and simian immunodeficiency virus (SIV). The microorganisms are identified by cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is treated to form (secondary) cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquaticus* DNA polymerase, *Thermus thermophilus* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid

may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et. al. (see entire reference) taught a method for cleaving an isolated nucleic acid where the nucleic acid was treated to form (secondary) cleavage structures. The cleavage structures were cleaved with a cleavage means. The cleavage means was an enzyme, which was a nuclease, which may be selected from the group consisting of *Thermos aquatics* (Tac) DNA polymerase and *Thermos thermophilous* (Tth) DNA polymerase. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of reference nucleic acid structures. The isolated nucleic acid may be a polymorphic locus which

may be isolated by polymerase chain reaction (PCR). The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus.

Lyamichev et. al. did not teach a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Lyamichev et. al. also does not teach that the microorganism may be a virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The reference does not teach that the detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. Lyamichev et. al. does not teach that the nucleic acid may comprise a nucleotide analog, where the nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The reference does not teach that the PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP, or the PCR primers from ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et. al. taught that this method can be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid.

Young, columns 3-4 and 10 taught the use of PCR with the nuclease *Thermos aquatics* (Tac) DNA polymerase to identify the polymorphic loci of ribosomal 16S RNA from

Mycobacterium spp. which increased the speed, accuracy and sensitivity of detection of disease causing microorganisms which were difficult to culture and could take up to several weeks to identify.

Seela and Roling, pages 55 and 61, taught the use of 7-deaza-dATP, 7-deaza-dGPT and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions.

Young et. al., on page 882, taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics, which was an effective means of direct detection of HCV that streamlined the procedure, reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

It would have been obvious to combine the teachings of Lyamichev et. al. with Young, Seela and Roling, and Young et. al. to produce a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The microorganisms are identified by cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is

treated to form (secondary) cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquatics* DNA polymerase, *Thermos thermophilous* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

It would have been obvious to combine these teachings because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. Seela and Roling recited the use of Tac polymerase with nucleotide analogs 7-

deaza-dATP, 7-deaza-dGPT and dUTP in PCR reactions. The use of these nucleotide analogs would have helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Young et. al. taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics. The use of Tth DNA polymerase in PCR was an effective means of direct detection of HCV which streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

One of ordinary skill in the art would have been motivated to combine the teachings of Lyamichev et. al. with Young, Seela and Roling, and Young et. al. to produce a method that could be used to optimize allele-specific PCR wherein the polymerase is also a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. The method used Tth DNA polymerase or Tac DNA polymerase with nucleotide analogs 7-deaza-dATP, 7-deaza-dGPT and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Also, the use of nuclease *Thermos thermophilous* DNA polymerase in PCR assays is an effective means of direct detection of HCV, which streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

6. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1805 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

September 2, 1997

DAVID GUZO
PRIMARY EXAMINER
GROUP 1800